NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Ustekinumab for the treatment of moderate to severe psoriasis

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to:

- provide further information on the randomisation method and numbers of participants in the clinical trials, the methods used to undertake the mixed treatment comparison and the subgroup analysis based on patient weight
- clarify the assumptions used in the cost effectiveness analysis and complete further economic analyses that did not include the patient access scheme and which used a 28-week stopping rule
- provide information about the time over which the patient access scheme would be available.

The European Medicines Agency has recommended that the marketing authorisation for efalizumab be suspended and NICE guidance on the use of efalizumab has been withdrawn. References to efalizumab in the NICE scoping documents, the manufacturer's submission and ERG report were made before the withdrawal of marketing authorisation.

Licensed indication

Ustekinumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and psoralen and long-wave ultraviolet radiation (PUVA).

Key issues for consideration

Clinical effectiveness

- The summary of product characteristics (SPC) for ustekinumab indicates that patients weighing more than 100 kg should receive a dose of 90 mg, while those weighing 100 kg or less should receive a dose of 45 mg. Which analysis (using all trial data or subgroup data) does the Committee consider to be most appropriate to estimate efficacy in these different groups of patients?
- Is improvement in psoriasis area and severity index (PASI) score (the outcome measure used in the economic analysis) an appropriate measure for treatment response? Should a measure of quality of life (such as the dermatology life quality index [DLQI]) be included?
- Does the Committee consider that the methods used in the mixed treatment comparison are appropriate?
- When comparing ustekinumab with etanercept, is it more appropriate to consider etanercept given intermittently (as recommended in NICE guidance) or continuously? What are the most appropriate assumptions for intermittent etanercept with regard to dose and efficacy?
- Does the Committee consider that the evidence from the clinical trial and mixed treatment comparison comparing ustekinumab with other biologic treatments is robust?
- What is the Committee's view of the potential short-term and long-term adverse events associated with the use of ustekinumab?

Cost effectiveness

- What does the Committee consider to be the most appropriate method for calculating utilities, as compared with those used in previous appraisals of biologic therapies?
- What are the most appropriate estimates to be assigned to key parameters in the model, including length of hospital stay for the management of severe psoriasis in non-responders and estimates of inpatient costs, as compared with those used in previous appraisals of biologic therapies?
- Does the Committee consider the exclusion of adverse events from the economic modelling to be appropriate?
- The estimates of cost effectiveness in the manufacturer's submission are conditional on the price of ustekinumab 90 mg being the same price as 45 mg (that is acceptance of the patient access scheme (PAS)). Does the Committee consider it appropriate to consider the estimates of cost effectiveness that include the patient access scheme?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	The manufacturer states that the submission addresses the clinical and cost effectiveness of treatment with ustekinumab within its licensed indication. Moderate to severe psoriasis is defined as a PASI score of ≥10 and DLQI score of >10. This definition is consistent with that used in previous NICE appraisals (TA103 and TA146) and in The British Association of Dermatologists guidelines.
Intervention	For people weighing 100 kg or less, ustekinumab is given as an initial dose of 45 mg administered subcutaneously at week 0, followed by a 45 mg dose at week 4, then every 12 weeks thereafter. For people with a body weight greater than 100 kg the dose is 90 mg administered subcutaneously at week 0, followed by a 90 mg dose at week 4, then every 12 weeks thereafter. The manufacturer provides two analyses. The first uses all data in the clinical trials. This includes patients weighing less than 100 kg who received 90 mg ustekinumab and patients weighing over 100 kg who received 45 mg ustekinumab (that is, dosing outside of the marketing authorisation). The second analysis includes subgroup data only for patients who received ustekinumab as per the marketing authorisation.
Comparators	Adalimumab: 80 mg initially, then 40 mg at week 1, and every 2 weeks thereafter Efalizumab: 0.7 mg/kg initially then 1 mg/kg every week Etanercept: 25 mg twice weekly administered continuously and intermittently; 50 mg twice weekly administered continuously for the first 12 weeks, then 25 mg twice weekly thereafter Infliximab: 5 mg/kg infused initially, repeated at 2 and 6 weeks following initial infusion and then every 8 weeks Supportive care (placebo)
Outcomes	The primary endpoint in the clinical trials is severity of psoriasis assessed by the PASI 75 score. Secondary outcomes include PASI 50 and 90, physician's global assessment (PGA) scores and health-related quality of life assessed using the DLQI. Adverse events are also reported for ustekinumab and comparators.

Economic evaluation	Quality adjusted life years (QALYs) are used in the economic analysis and are derived through mapping DLQI measurements to EQ-5D UK tariff scores for PASI response categories. The model includes the biologic therapies and best supportive care. The time horizon (10 years) applied in this submission reflects that used in previous submissions for biologics in psoriasis. Costs are estimated from the perspective of the NHS.

1.2 Evidence Review Group comments

1.2.1 Population

The population described in the decision problem appears appropriate for the NHS.

1.2.2 Intervention

Ustekinumab was licensed in January 2009 for the treatment of moderate to severe plaque psoriasis in adults who have had an inadequate response to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA. The marketing authorisation includes weight-based dosing of ustekinumab. People weighing more than 100 kg should receive 90 mg while those weighing 100 kg or less should receive 45 mg.

1.2.3 Comparators

The comparator interventions described in the decision problem appear to be appropriate for the NHS. However, the doses of etanercept include doses and dosing schedules (that is, 25mg twice weekly administered continuously, and 50mg administered twice weekly for the first 12 weeks, followed by 25mg thereafter) which are not recommended by NICE (see appendix B).

1.2.4 Outcomes

The PASI is used in all trials as an outcome measure and this is reflected in the MS. The PASI is not an ideal measure of the severity of psoriasis and its limitations are well documented; however it is often the best measure available.

1.3 Statements from professional/patient groups and nominated experts

The clinical specialists suggested that the technology should be used in secondary care, prescribed only by dermatologists who are experienced in immunotherapy and treating severe psoriasis. They noted that support may be required by biologics nurses and community services such as Healthcare at Home for advice, monitoring and instruction in administration of therapy. However, because it is only given once every 3 months, the person could be scheduled to attend their routine dermatologist clinic appointment and receive the injection there, potentially removing the need for community services. This might also aid compliance.

The patient experts indicated that people who are needle phobic or who cannot self-inject would need assistance to administer ustekinumab.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer presented data from three randomised controlled trials (RCTs) that reported the efficacy of ustekinumab for the treatment of adults with moderate to severe chronic plaque psoriasis. Two of the RCTs compared ustekinumab with placebo (PHOENIX-1 and PHOENIX-2) and one compared ustekinumab with etanercept (ACCEPT). The PHOENIX-1 and PHOENIX-2 trials are ongoing with a planned follow-up duration of 5 years. The ACCEPT trial is a 64-week study and is also ongoing with 12-week data reported in the manufacturer's submission.

Summary details of the three studies are presented in table 1.

Table 1 Summary of ustekinumab trials

Trial name	Design and duration	Participants	Intervention and comparator (n =)	Primary outcome
PHOENIX-1	5 years Phase III RCT Multicentre	Adult patients with moderate to severe plaque psoriasis for ≥ 6 months; ≥ 10% BSA involvement, PASI ≥ 12; have received prior systemic therapy or were candidates for such therapy	Ustekinumab sc 45 mg n=255 90 mg n=256 Placebo n=225	% patients with PASI 75 at week 12
PHOENIX-2	5 years Phase III RCT Multicentre	Adult patients with moderate to severe plaque psoriasis for ≥ 6 months; ≥ 10% BSA involvement, PASI ≥ 12; have received prior systemic therapy or were candidates for such therapy	Ustekinumab sc 45 mg n=409 90 mg n=411 Placebo n=410	% patients with PASI 75 at week 12
ACCEPT	64 weeks Phase III Multicentre	Adult patients with moderate to severe plaque psoriasis for ≥ 6 months; ≥ 10% BSA involvement, PASI ≥ 12; have received prior systemic therapy or were candidates for such therapy	Ustekinumab sc 45 mg n=209 90 mg n=347 Etanercept 50 mg twice weekly n=347	% patients with PASI 75 at week 12

Abbreviations: BSA, body surface area; PASI, psoriasis area and severity index; sc, subcutaneous.

The PHOENIX trials reported that after a 12-week follow-up, ustekinumab in comparison with placebo was effective in improving psoriasis across multiple outcome measures including PASI and PGA. In the PHOENIX-1 trial, the percentage of patients who achieved a PASI 75 response at week 12 was 67%, 66% and 3% in the ustekinumab 45 mg, 90 mg groups and placebo, respectively. In the PHOENIX-2 trial, the percentage of patients who achieved

a PASI 75 response at week 12 was 67%, 76% and 4% in the ustekinumab 45 mg, 90 mg and placebo groups, respectively (see pages 47–51 of the MS).

In addition, there was a statistically significant improvement in patients' quality of life as measured by the DLQI (see page 48 and 50 of the MS). The PHOENIX trials reported that the PASI response rates observed during the double-blind, randomised phases of the studies were maintained in the longer term (see page 55 of the MS).

The ACCEPT trial reported that after a 12 week follow-up both ustekinumab 45 mg and ustekinumab 90 mg were statistically significantly more effective than etanercept 50 mg twice weekly. Of the patients treated with ustekinumab 45 mg and ustekinumab 90 mg, 68% and 74% respectively achieved a PASI 75 response compared with 57% of those treated with etanercept 50 mg twice weekly. A statistically significantly higher proportion of patients treated with ustekinumab 45 mg and ustekinumab 90 mg also achieved a PGA of cleared or minimal (65% and 71% respectively) compared with etanercept 50 mg twice weekly (49%). In addition, the results of the ACCEPT trial demonstrated that statistically significantly more patients achieved a PASI 90 response at week 12 for both ustekinumab groups (36% and 45% for ustekinumab 45 mg and ustekinumab 90 mg respectively) versus the etanercept group (23%; see pages 52–53 of the MS).

The manufacturer reported that efficacy was consistent across all identified subpopulations including demographic and disease characteristics, previous treatment (see page 88–89 of the MS).

The manufacturer reports an analysis of subgroup data that suggests that ustekinumab 90 mg is a more effective dose than 45 mg for patients who weigh more than 100 kg. In the PHOENIX-1 trial, 68% of patients weighing more than 100 kg who received ustekinumab 90 mg achieved a PASI 75 at 12 weeks compared to 54% of those who received ustekinumab 45 mg. In the

PHOENIX-2 trial, it was 71% and 49% respectively (see table 16, page 42 of the ERG report). A graph of PASI 75 response rates by 10kg weight increments after a follow-up of 28 weeks is shown on page 102 of the MS.

The manufacturer reported that ustekinumab was generally well tolerated across all three phase III studies. In the PHOENIX-1 trial the percentage of patients having one or more adverse events was 57.6%, 51.4% and 48.2% in the ustekinumab 45 mg, 90 mg and placebo groups respectively. The proportion of patients having a serious adverse event was 0.8%, 1.6% and 0.8% in the ustekinumab 45 mg, 90 mg and placebo groups respectively. Similar rates of adverse events were reported in the PHOENIX-2 trial (see page 44 of the ERG report). In the ACCEPT trial the percentage of patients having one or more adverse events was 66%, 68.3% and 69.5% in the ustekinumab 45 mg, 90 mg and etanercept groups respectively. The proportion of patients having a serious adverse event was 1.9%, 1.2% and 1.2% in the ustekinumab 45 mg, 90 mg and etanercept groups respectively (see page 45 of the ERG report).

The manufacturer undertook a mixed treatment comparison (MTC) to compare the effectiveness of ustekinumab with other treatment options for moderate to severe psoriasis. The MTC included 20 studies. A network diagram for the MTC is included on page 88 of the ERG report. The comparison followed the methodology used by the Assessment Group in the Multiple Technology Appraisal of efalizumab and etanercept (see NICE technology appraisal guidance 102) and subsequently used in the Single Technology Appraisals of adalimumab (see NICE technology appraisal guidance 146) and infliximab (see NICE technology appraisal guidance 134). The MS states that a fixed effects baseline was used (see page 59 of the MS). However, the manufacturer subsequently clarified that a random effects baseline model was used. The code included in the report by the Assessment Group for the appraisal of efalizumab and etanercept indicates that a random effects baseline model has also been used in previous appraisals.

The results of the manufacturer's MTC are presented below (tables 2 and 3). Results from this analysis suggest that after infliximab, ustekinumab has the highest mean PASI 75 response rate. The results of the manufacturer's MTC for relative risk of PASI response are on pages 75–76 of the MS. The results for ustekinumab in table 2 includes only those patients who received 45 mg if ≤ 100 kg and 90 mg if > 100 kg (weight-based dosing, page 75 of the MS).

Table 2 Probability of response based on weight-based dosing for ustekinumab

Treatment	PASI 50			PASI 75			PASI 90		
	Mean	2.5%	97.5%	Mean	2.5%	97.5%	Mean	2.5%	97.5%
Supportive care/placebo	13%	12%	14%	**4%**	3%	4%	1%	0%	1%
Ustekinumab 45 mg	[redacted]								
Etanercept 50 mg	77%	71%	81%	**52%**	46%	59%	24%	19%	30%
Ustekinumab 90 mg	[redacted]								
Efalizumab	51%	45%	58%	**26%**	21%	32%	8%	6%	11%
Etanercept 25 mg	64%	56%	71%	**38%**	30%	45%	14%	10%	19%
Infliximab	94%	90%	96%	**80%**	73%	86%	54%	44%	63%
Adalimumab	81%	75%	87%	**59%**	50%	68%	30%	22%	39%

Table 3 Probability of response for all patients (page 76 of the MS)

Treatment	PASI 50			PASI 75			PASI 90		
	Mean	2.5%	97.5%	Mean	2.5%	97.5%	Mean	2.5%	97.5%
Supportive care/placebo	13%	12%	14%	**4%**	3%	4%	1%	0%	1%
Ustekinumab 45 mg	88%	84%	91%	**69%**	62%	75%	40%	33%	48%
Etanercept 50 mg	76%	71%	81%	**52%**	45%	59%	24%	19%	30%
Ustekinumab 90 mg	90%	87%	93%	**74%**	68%	80%	46%	39%	54%
Efalizumab	51%	45%	58%	**26%**	21%	32%	8%	6%	11%
Etanercept 25 mg	65%	56%	73%	**39%**	30%	48%	15%	10%	21%
Infliximab	93%	89%	96%	**80%**	70%	87%	54%	42%	64%
Adalimumab	81%	74%	87%	**58%**	49%	68%	30%	23%	39%

2.2 Evidence Review Group comments

Overall, the ERG concluded that the MS provided an unbiased estimate of the clinical effectiveness of ustekinumab at 12 weeks based on the results of the three randomised comparisons. However, they noted the following issues:

- There is a lack of information regarding the methodology used for the weight-based subgroup analysis. The ERG could not determine whether the methods used were appropriate and whether the subgroup analysis supports the weight-based categorisation presented. The ERG could not establish whether the sample sizes were adequate for these analyses.
- It is unclear whether there is any impact from the use of a fixed effect baseline model rather than the random effects baseline model.
- The submission includes only minimal discussion of any possible clinical heterogeneity between the trials included in the MTC.
- In the MTC, data from the weight-based dosing analysis of ustekinumab was taken from a subgroup of the trial data, whereas for the comparator trials all patient data were used.
- Because of the above factors, the clinical effectiveness of ustekinumab in comparison with other drugs used for the treatment of moderate to severe psoriasis is uncertain.

2.3 Statements from professional/patient groups and nominated experts

The clinical specialists considered that ustekinumab would be an effective treatment for psoriasis. They considered that ustekinumab may be more effective than etanercept and adalimumab, although it may be less effective than infliximab. Ustekinumab has a longer median time to relapse than other biologics. This gives convenience of administration as it can be administered once every 12 weeks.

The clinical specialists noted that overall, the rates of adverse events for ustekinumab were similar to those for placebo and there was no consistent evidence of a relationship between the dose and the occurrence of adverse events. The clinical specialists considered that the nature of the adverse events were similar to those expected from a biological therapy, including upper respiratory tract infection, nasopharingitis, arthralgia, cough and headache.

The patient experts highlighted the convenience of a treatment that is administered once every 12 weeks. They considered that this would provide freedom to patients and may lead to better compliance. The patient experts considered that an effective treatment with less frequent administration could improve physical symptoms as well as social functioning.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer's cost-effectiveness analysis was based on a previous analysis undertaken by Woolacott et al. (2006) for the appraisal of etanercept and efalizumab for the treatment of psoriasis ('The York model'). The York model was updated with the results of the MTC undertaken by the manufacturer. The manufacturer stated that the model included only biologics and supportive care – not conventional systemic therapies – because

biologics are only recommended after people have had an inadequate response to conventional systemic treatment (that is, methotrexate, ciclosporin and PUVA).

Ustekinumab is modelled as per its licensed indication for treatment of moderate to severe plaque psoriasis. The base-case analysis is a weighted average of the 45 mg and the 90 mg doses (assuming that 20% of people weigh more than 100 kg and receive ustekinumab 90 mg [see page 102 of the MS]). There is a trial period for all the interventions (12 weeks for etanercept and efalizumab, 10 weeks for infliximab and 16 weeks for ustekinumab and adalimumab), after which the person will only continue therapy if they achieve a PASI 75 response. For ustekinumab the model uses 12 week trial data to reflect 16 week response rates, and it is assumed that the efficacy of ustekinumab does not decline between 12 weeks and 16 weeks (see figure 6.4.1, page 55 of the MS). If a person's psoriasis has responded to treatment at the end of the trial period (that is, achieved a PASI 75 response), they will then continue on treatment for a maximum of 10 years (the 'treatment' period). An annual dropout rate of 20% is applied to all treatments over the time horizon of the model, reflecting the assumption used in the York model. The mean time on treatment for a person who responds to treatment is 3.65 years.

The manufacturer included a reduction in efficacy for intermittent etanercept in comparison with continuous etanercept based on results of a study by Moore et al that showed reduced response at 12 weeks in patients who received intermittent etanercept compared with those who received continuous etanercept. In the model it was assumed that 81% of patients who received intermittent etanercept would maintain their initial treatment response, and 19% would experience a reduction in response of one PASI level (see page 110 of the MS).

Adverse events are not directly included in the economic evaluation but the manufacturer stated that these have been considered indirectly by response rates and the estimation of annual dropout. The manufacturer stated that the

direct inclusion of adverse events would be unlikely to affect the estimated cost effectiveness of ustekinumab, since adverse events were infrequent and similar to those observed in the placebo groups in the phase III trials.

3.1.1 Resource use and utilities

The cost and resource use data were obtained from the Woolacott et al. report, Healthcare Resource Group (HRG) NHS reference costs, the 'British national formulary' (BNF 56, 2008) and PSSRU Unit Costs of Health and Social Care 2007. Costs were analysed from the perspective of the NHS in England and Wales. Resource utilisation was based on the patient population specified in the respective SPCs, The British Association of Dermatologists guidelines for the treatment of psoriasis, published literature, UK national databases and clinical specialist opinion. Drug dosage and costs were based on the September 2008 edition of the BNF (see page 118 of the MS). In the model, the cost of ustekinumab is £2,147 per dose. The manufacturer calculates that the total cost of treatment with ustekinumab in the trial period (that is the first 16 weeks of treatment) is £4,294 and that the annual cost thereafter is £9,637. This figure includes drug, monitoring and outpatient costs (see page 121 and 122 of the MS).

Following the latest guidelines from The British Association of Dermatologists for the use of biological interventions in psoriasis, the manufacturer assumed that treatment would be started and monitored by a consultant dermatologist experienced in psoriasis. In addition, to educate people to self-inject, three 1-hour sessions of staff nurse time were costed during the initial trial period. The above assumptions, also used in the Woolacott et al. analysis, are common to all biologics administered subcutaneously included in the analysis. In line with previous NICE appraisals of biologics for the treatment of psoriasis and in consultation with clinical specialists, the manufacturer assumed that there would be one hospitalisation per year for people who did not respond to treatment. The length of stay for this inpatient admission is estimated to be 21 days, as used in the York model.

The utilities in the model were based on the proportion of people in the different PASI categories and the change in utility from baseline associated with these PASI response categories (< PASI 50, PASI 50–PASI 75, PASI 75–PASI 90, > PASI 90), adjusted for baseline DLQI. These were estimated from an original analysis of patient-level data from PHOENIX-1 and PHOENIX-2 and a replica of the EQ5D–DLQI regression based on the scatter-plot published in the HTA report. The calculation of the utilities estimates consisted of two stages, described below.

First, the mean change in the DLQI score between baseline and week 12 was estimated for patients from the PHOENIX trials, with different levels of PASI response. In contrast to the York model, the manufacturer used only patients with a baseline DLQI ≥10 in line with the eligible population for biologics. The results are presented in table 4.

Table 4 Mean change in DLQI between baseline and week 12 by PASI response and baseline DLQI (page 114 of the MS)

PASI response	n	Mean change in DLQI (SD)
< 50	430	-2.5 (6.7)
≥ 50 and < 75	160	-10.3 (6.1)
≥ 75 and < 90	207	-13.4 (5.8)
≥ 90	318	-15.3 (5.6)
All	1,115	-9.3 (8.3)

In the second stage, an ordinary least squares (OLS) linear regression analysis of the DLQI–EQ5D data from the Health Outcomes Data Repository (HODaR) database was undertaken to estimate the mean gain in utility for the various PASI response categories. Although results were deemed confidential and were not reported in the Woolacott et al. report, the manufacturer estimated the coordinates in the published scatter-plot in order to replicate the regression and predict the relationship between DLQI and EQ-5D.

The results of the OLS linear regression can be seen in figure 7.2.3 of the MS (page 115). Estimated mean utility gains associated with PASI response categories, conditional on baseline DLQI severity, are reported in table 5.

Table 5 Estimated utility gains for the different PASI response categories (see page 115 of the MS)

PASI response	All patients
< 50	0.04
≥ 50–< 75	0.17
≥ 75–< 90	0.22
≥ 90	0.25

Alternative utility values were calculated using SF-36 data collected in the PHOENIX-1 trial converted to SF-6D utility scores. These utility values were used in a sensitivity analysis (see pages 117 and 124 of the MS).

3.1.2 Patient access scheme

The SPC recommends that people whose weight exceeds 100 kg should receive 90 mg of ustekinumab. This is double the cost of the 45 mg that is required to treat a person who weighs 100kg or less. To address this inequality, the manufacturer has proposed a patient access scheme to the Department of Health. In the scheme, people who weigh more than 100 kg and who are prescribed the 90 mg dose (2 x 45mg vials) will receive both vials at a total cost of £2,147. The manufacturer has proposed that this access scheme will be available to the NHS at least until any re-review of the guidance by NICE or the introduction of any new formulations that would render the scheme obsolete.

3.1.3 Cost effectiveness results

The manufacturer's base-case analysis assumes a weighted average of the weight-based dosing where 80% of people receive ustekinumab 45mg and 20% of people receive ustekinumab 90mg. This analysis also assumes that the patient access scheme is in place. The incremental cost-effectiveness

ratio (ICER) for ustekinumab versus supportive care was estimated to be £29,587 per QALY gained. The ICER for ustekinumab versus intermittent etanercept 25 mg was estimated to be £27,105[1] per QALY gained. Ustekinumab dominated (that is, was associated with more QALYs and lower costs) all other treatments except infliximab (see page 126 and table 7.3.2, page 127 of the MS). The results from the base-case analysis are shown in table 6.

Table 6 Base-case results (weighted average – weight by dose for ustekinumab) – deterministic (page 126 of the MS)

Comparator	Mean QALY difference compared with supportive care	Mean costs difference compared with supportive care	ICER for ustekinumab vs treatment in first column	ICER for each drug in the first column vs supportive care
Supportive care	0	£0	£29,587	-
Efalizumab	0.1308	£5,264	Dominant	£40,250
Etanercept 25 mg intermittent	0.1325	£3,989	£27,105	£30,019
Etanercept 25 mg continuous	0.1409	£4,829	Dominant	£34,281
Etanercept 50 mg continuous	0.1483	£5,333	Dominant	£35,964
Adalimumab	0.1502	£4,660	Dominant	£31,022
Ustekinumab	**0.1560**	**£4,615**	**-**	**£29,587**
Infliximab	0.1616	£6,327	£304,566*	£39,153

* this ICER compares infliximab to ustekinumab. Therefore, for willingness-to-pay thresholds up to £30,000 ustekinumab is the favoured option over infliximab

Probabilistic sensitivity analysis suggested that the probability of ustekinumab being cost effective at £20,000 and £30,000 per QALY gained was 7.4% and 48.5% respectively. The submission suggests that ustekinumab has the highest probability of being cost effective and that other biologics have a zero probability of being cost effective (see page 75 of the ERG report).

[1] The estimates of incremental cost effectiveness in the premeeting briefing are taken from the errata provided by the manufacturer and therefore differ from those in the manufacturer's submission.

The manufacturer completed a series of one-way sensitivity analyses (see page 132 of the MS). Using SF-6D utility values instead of DLQI-based utility values increased the ICER for ustekinumab in comparison with supportive care from £29,587 to £49,371 per QALY gained (see page 131 of the MS). Varying the assumption about the efficacy of intermittent etanercept relative to the efficacy of continuous etanercept from the base case value of 81% to 71% and 91%, produced ICERs for ustekinumab compared with etanercept 25 mg intermittent of £22,634 and £32,949 per QALY gained.

The manufacturer conducted a subgroup analysis of the clinical trial data to reflect the weight-based dosing suggested in the SPC (that is using ustekinumab 45mg for patients under 100kg and ustekinumab 90mg in patients over 100kg). These analyses assume that the patient access scheme is in place. The results of this analysis suggest that ustekinumab when compared with supportive care results in an ICER of £29,334 for ustekinumab 45 mg and £30,693 for ustekinumab 90 mg. In this analysis, ustekinumab 45 mg dominates all other treatment options (that is gives greater benefit for less cost) when compared to the other biologic agents, apart from intermittent etanercept 25 mg, where the ICER is estimated to be £25,468, and infliximab, where the ICER is £334,423 per QALY gained. Ustekinumab 90 mg has an ICER of £34,897 compared with intermittent etanercept 25 mg and it dominates all other biologic agents except adalimumab and infliximab. The results for the weight-based dosing analysis are shown in table 7.

Table 7 Weight-based dosing for ustekinumab – deterministic (page 130 of the MS)

Comparator	Mean QALY difference compared with supportive care	Mean costs difference compared with supportive care	ICER for ustekinumab vs treatment in first column	ICER for each drug in the first column vs supportive care	Comparator
Supportive care	0	£0	£29,334	£30,693	-
Efalizumab	0.1308	£5,264	Dominant	Dominant	£40,250
Etanercept 25 mg intermittent	0.1325	£3,989	£25,468	£34,897	£30,019
Etanercept 25 mg continuous	0.1409	£4,829	Dominant	Dominant	£4,281
Etanercept 50 mg continuous	0.1483	£5,333	Dominant	Dominant	£35,964
Adalimumab	0.1502	£4,660	Dominant	£18,204	£31,022
Ustekinumab 90mg	**0.1542**	**£4,732**	**Dominant**		**£30,693**
Ustekinumab 45mg	**0.1564**	**£4,588**		**Dominated**	**£29,334**
Infliximab	0.1616	£6,327	£334,423*	£216,081*	£39,153

* this ICER compares infliximab to ustekinumab. Therefore, for conventional willingness to pay thresholds,ustekinumab is favoured over infliximab

3.2 Evidence Review Group comments

The ERG identified a number of issues relating to the uncertainty around the estimates of cost effectiveness. These are detailed below.

- Clinical effectiveness estimates used in the MS base case and weight-based dosing analyses are contingent on accepting that the methodology for the weight-based analyses is appropriate and that the subgroup is also appropriate.

- There is uncertainty about the estimate of relative efficacy between intermittent and continuous etanercept 25 mg. Ustekinumab becomes more cost effective in comparison with intermittent etanercept as the

relative efficacy of intermittent etanercept compared with continuous etanercept decreases.

- The estimates of utility based on the SF-36 patient level data are lower in comparison with the DLQI-based EQ-5D estimates. It is uncertain which set of utility gains presented in the model are the most accurate in terms of validity and generalisability.

- Non-responders are assumed to have an annual inpatient admission of 21 days associated with supportive care. This is an important assumption as the costs of biological treatment are offset by reductions in supportive care costs. The MS does not provide sufficient details about the method of calculating the estimated cost per bed day.

- The assumption that the efficacy of ustekinumab at 16 weeks is the same as at 12 weeks is conservative only if there is evidence of a non-declining trend in the rates of PASI 75 response in the period between the 12th and the 16th weeks from baseline.

- Expert opinion was used to determine the frequency of outpatient visits and laboratory tests associated with ustekinumab treatment. The MS does not provide sufficient information about the way the experts were identified and the method of elicitation of experts' opinion.

- The probabilistic sensitivity analysis appears to include only variables for utilities, treatment response and the proportion of patients weighing more than 100 kg. It does not include variables in the PSA which were shown to be influential in one-way sensitivity analyses, for example the number of hospital days, the effect of different inpatient costs and the effectiveness of intermittent etanercept.

3.2.1 ERG exploratory analyses

The ERG completed an exploratory analysis for the base-case analysis using the price for ustekinumab 90 mg as double the list price of ustekinumab 45 mg

(that is, assuming there is no patient access scheme in place). The ERG analyses were completed before the manufacturer submitted the errata for intermittent etanercept. Therefore these exploratory analyses do not include any amendments made to the efficacy of intermittent etanercept. The results are presented in table 8 and show that the ICER for ustekinumab compared with supportive care increases to £40,952 per QALY gained (see page 70 of the ERG report).

Table 8 Ustekinumab deterministic results with ustekinumab 90 mg costed at twice price of ustekinumab 45 mg (page 70 of the ERG report)

Comparator	Mean QALY difference compared with supportive care	Mean costs difference compared with supportive care	ICER for ustekinumab vs treatment in first column	ICER for each drug in the first column vs supportive care
Supportive care	£0	0.0000	40,952	-
Etanercept 50 mg	£5,333	0.1483	137,323	35,964
Etanercept 25 mg	£3,989	0.1325	102,034	30,111
Etanercept 25 mg continuous	£4,829	0.1409	103,157	34,281
Efalizumab	£5,264	0.1308	44,597	40,250
Infliximab	£6,327	0.1616	Dominated	39,153
Adalimumab	£4,660	0.1502	300,063	31,022
Ustekinumab	£6,387	0.1560	-	40,952

The ERG also completed an exploratory analysis using the efficacy data from all patients according to the dose of ustekinumab received regardless of weight and assuming the price for ustekinumab 90 mg is double the list price of ustekinumab 45 mg. The results are presented in table 9 and show that the ICER for ustekinumab 45 mg compared with supportive care is £29,334 per QALY gained, while that for ustekinumab 90 mg is £88,417 per QALY gained (see page 70 of the ERG report).

Table 9 Efficacy data from all patients according to their randomisation outcome, and assuming the price of ustekinumab 90 mg is double the price of ustekinumab 45 mg (page 70 of the ERG report)

Comparator	QALY difference compared with supportive care	costs difference compared with supportive care	ICER ustekinumab 45 mg vs treatment in first column	ICER ustekinumab 90 mg vs other drugs	ICER for each drug in the first column vs supportive care
Supportive care	£0	£0	29,334	88,417	-
Etanercept 50 mg	0.1483	£5,333	Dominant	1,411,694	35,964
Etanercept 25 mg intermittent	0.1325	£3,989	25,035	444,131	30,111
Etanercept 25 mg continuous	0.1409	£4,829	Dominant	661,382	34,281
Efalizumab	0.1308	£5,264	Dominant	357,606	40,250
Adalimumab	0.1502	£4,660	Dominant	2,266,322	31,022
Ustekinumab 45 mg	0.1564	£4,588	-	Dominated	29,334
Ustekinumab 90 mg	0.1542	£13,631	Dominant	-	88,417
Infliximab*	0.1616	£6,327	£334,205*	Dominated	39,153

. * this ICER compares infliximab to ustekinumab

The ERG conducted three further exploratory sensitivity analyses. The first varied the proportion of people weighing more than 100 kg. In the PHOENIX-1 trial, 35% of participants weighed more than 100 kg, and the ERG used this as the highest estimate included in the analysis. In this analysis it was also assumed that the price for ustekinumab 90 mg is double the list price of ustekinumab 45 mg. The ICER for ustekinumab increased to between £38,000 and £50,000 versus supportive care when the proportion of people weighing more than 100 kg varied between 15% and 35% (see table 29, page 71 of the ERG report).

The second analysis varied the total cost of an inpatient admission incurred by people in supportive care. This analysis varied the cost of an inpatient admission from £5,000 to £6,500. The ICER for ustekinumab in comparison

with supportive care ranged from £27,514 to £34,639 per QALY gained (see table 30, page 71 of the ERG report).

A further analysis assumed that the efficacy of intermittent etanercept 25 mg was the same as for continuous etanercept 25 mg. Under this assumption, the ICER of ustekinumab compared with intermittent etanercept 25 mg in the base-case analysis was £41,449 per QALY gained (see page 73 of the ERG report).

Finally, the ERG conducted a probabilistic sensitivity analysis that included a larger number of variables than were included by the manufacturer. The results of the analysis suggested greater uncertainty around the estimates of cost effectiveness, but the cost effectiveness acceptability curves did not differ significantly from those of the manufacturer (see page 75 and 77 of the ERG report). When the ERG repeated the analysis assuming that the cost of ustekinumab 90 mg was twice that of ustekinumab 45 mg, the probability of ustekinumab being cost effective was zero.

4 Authors

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Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessment Centre (SHTAC):

- Gospodarevskaya E, Picot J, Cooper K et al

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Janssen-Cilag

II Professional/specialist, patient/carer and other groups:

- British Association of Dermatologists
- Royal College of Physicians
- Psoriasis Association
- Psoriasis and Psoriatic Arthritis Alliance
- Dorset PCT

C Additional reference used:

- Woolacott N, Bravo VY, Hawkins N, et al. (2006) Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technology Assessment; 10(31): iii-239.

Appendix B: Previous NICE guidance

'Etanercept and efalizumab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 103, July 2006).

Key points of guidance:

- Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met.
  - The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10.
  - The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments.
- Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either:
  - a 75% reduction in the PASI score from when treatment started (PASI 75) or
  - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started.
- Efalizumab, within its licensed indications, is recommended for the treatment of adults with plaque psoriasis under the circumstances detailed as for etanercept only if their psoriasis has failed to respond to etanercept or they are shown to be intolerant of, or have contraindications to, treatment with etanercept. Further treatment with efalizumab is not recommended in patients unless their psoriasis has responded adequately

at 12 weeks. It is recommended that the use of etanercept and efalizumab for psoriasis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis. If a person has both psoriasis and psoriatic arthritis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.

'Infliximab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 134, January 2008).

Key points of guidance

- Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met.
  - The disease is very severe as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more and a Dermatology Life Quality Index (DLQI) of more than 18.
  - The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant to or has a contraindication to these treatments.
- Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either:
  - a 75% reduction in the PASI score from when treatment started (PASI 75) or
  - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started.
- When using the DLQI healthcare professionals should take care to ensure that they take account of a patient's disabilities (such as physical impairments) or linguistic or other communication difficulties, in reaching conclusions on the severity of plaque psoriasis. In such cases healthcare

professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with section 1.2

'Adalimumab for treatment of moderate to severe psoriasis' (NICE technology appraisal guidance 146, July 2008)

Key points of guidance

- *Adalimumab is recommended as a treatment option for adults with plaque psoriasis for whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met.*
  - The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10.
  - The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant of, or has a contraindication to, these treatments.
- Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either:
  - a 75% reduction in the PASI score (PASI 75) from when treatment started, **or**
  - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment.
- When using the DLQI, healthcare professionals should ensure that when reaching conclusions on the severity of plaque psoriasis they take into account a person's disabilities (such as physical impairments) and linguistic or other communication difficulties. In such cases, healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a

decision about whether to continue the use of adalimumab in accordance with section 1.2.